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FROM Lisa B. Kole, Ph.D., M.D., J.D.
DATE April 26, 2007
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MESSAGE

RE: REISSUE PATENT 5,688,657
REISSUE SERIAL NO. 09/633,034

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PAGE 1/8 * RCVD AT 4/26/2007 4:37:12 PM [Eastern Daylight Time] * SVR:USPTO-EFAX-1/3 * DNIS:2730834 * CSID: * DURATION (mm-ss):03-02

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Reissue Application For: United States Patent No. 5,688,657
Title: MONOCLONAL ANTIBODIES AGAINST
CARCINOMA-ASSOCIATED ANTIGENS
AND USES THEREFOR
Patent Appln. Filed: September 12, 1994
Patent Issued: November 18, 1997
Assignee: International Bio-Immune Systems, Inc.
Patent Group Art Unit: 1652
Reissue Applicants: Kwong Y. Tsang and Myron Arlen
Reissue Serial No. 09/633,034 Art Docket No. 33081-R 072771.0106
Reissue Appln Filed: August 4, 2000

SUPPLEMENTARY REISSUE DECLARATION BY ASSIGNEE

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SIR:

International Bio-Immune Systems, Inc.(hereafter, "IBS"), as the assignee of the entire right, title and interest in United States Patent No. 5,688,657, on which the above-identified reissue application is based, declares as follows.

IBS is a corporation having an address at 225 West Community Drive, Suite 140, Great Neck, New York 11021. IBS believes that the above-identified reissue application does not seek to enlarge the claims of the original patent.

I. REVIEW OF PAPERS AND DUTY OF CANDOR

IBS has reviewed and understands the contents of the above-identified patent, including the issued claims, and the above-identified reissue application, including the claims thereof.

IBS acknowledges the duty to disclose information which is material to the patentability of this reissue application, in accordance with 37 C.F.R. §1.56.

II. PRIORITY CLAIM

The above-identified reissue application is based on the '657 patent which is a continuation-in-part of Serial No. 08/159,836, filed November 30, 1993, now abandoned, which is a continuation-in part of Serial No. 08/117,430, filed September 7, 1993, now abandoned, which is a continuation-in-part of Serial No. 07/670,816, now abandoned, which is a continuation-in-part of Serial No. 07/176,337, filed March 31, 1988, now abandoned.

III. OFFER TO SURRENDER ORIGINAL LETTERS PATENTS

IBS hereby offers to surrender the original letters patent, or provide an appropriate affidavit or declaration in the event that the original patent is lost, upon an indication of allowability of this reissue patent application.

IV. STATEMENT OF INOPERATIVENESS OF THE ISSUED PATENT

IBS believes the original patent to be wholly or partly inoperative because of several errors that arose without any deceptive intention on the parts of applicants therefor.

First, inadvertent errors during the prosecution of the application that issued as the '657 patent resulted in erroneous deposits of the hybridoma cell lines referred to in the patent as PCA 31.1 and PCA 33.28, corresponding to ATCC Accession Nos. HB-12314 and HB-12315, respectively. Second, the specification and claims indicate that the colon carcinoma-associated antigens identified do not occur on any carcinomas other than colon carcinoma, when the specification provides data that indicates that these antigens are indeed present on certain other forms of human carcinoma (but not normal tissue). Third, claims 22, 23 and 47 erroneously state that the target antigen in a test sample is "purified," which makes these claims wholly or partly inoperative.

Each of these inadvertent errors are discussed in greater detail below.

V. SPECIFICATION OF "ERRORS" RELIED UPON AND HOW THEY AROSE

The following is a description of the manner in which the errors specified below are believed to have occurred.

First, with regard to the erroneous deposits, on March 13, 1997, to enable claims directed towards monoclonal antibodies 31.1 and 33.28, IBS deposited, with the American Type Culture Collection ("ATCC"), what were believed to be the murine hybridoma cell lines PCA 31.1 and PCA 33.28 that produce, respectively, monoclonal antibodies mAb 31.1 and 33.28. The deposited cell lines were assigned accession numbers HB-12314 and HB-12315, respectively.

In September, 1998, Purdue Pharma, a licensee of the '657 patent, requested a sample of the murine 31.1 antibody. IBS thereafter supplied Purdue a sample of antibody, now believed to be produced by the same hybridoma cell line deposited with the ATCC and assigned accession number HB-12314. In October and November of 1998, Purdue Pharma presented data indicating that presumed 31.1 antibody did not have the expected biological properties, i.e., it did not compete with an antibody known to bind to the same antigen recognized by the 31.1 antibody.

Concerned about the identity of the murine hybridoma cell line, IBS obtained the DNA sequence encoding a portion of the variable heavy chain region of the monoclonal antibody secreted by the cell line and determined that the cell line was not producing the expected 31.1 antibody. With regard to the 33.28 antibody, when immunohistochemical studies were performed, the secreted antibody was found not to have the expected immunospecificity.

It is now believed that an employee of IBS had, without deceptive intent, mistakenly mislabeled tubes believed to contain both the murine hybridoma cell lines producing the 31.1 and 33.28 monoclonal antibodies when preparing frozen samples of the cells for storage purposes. The samples of hybridoma cells deposited with the ATCC are believed to have been prepared from cultures derived from mislabeled frozen cells, thus resulting in erroneous deposits of the HB-12314 and HB-12315 hybridoma cell lines referred to in the '675 patent.

Accordingly, the mAbs made available via the ATCC depository are believed not to be the monoclonal antibodies claimed, and hence the specification of the '657 patent is defective.

In addition, the specification and claims of the '657 patent erroneously state, at various sections of text, that the colon carcinoma associated antigens generally claimed are not found on human carcinoma cells other than colon carcinoma cells (see, for example, the specification at column 3, lines 58-62 and claims 1, 30, 34 and 38). These statements are contradicted by statements and data presented in the '657 patent specification, including (1) the patent specification at column 4, lines 33-35, which states "the antigens are tumor specific, being present in the malignancies of colon, *breast and ovarian cancer*" (emphasis added); (2) Example XI at column 29, line 61 through column 30, line 12, which states that "[t]hese results indicate that the antigens defined by mAbs 31.1 and 33.28 are expressed in a select group of women with breast disease and would be useful for diagnosis of said disease;" and (3) Example XII at column 30, lines 15-20, which states that "[t]hese results indicate that the antigens defined by mAbs 31.1 and 33.28 are expressed in a select group of women with ovarian cancer and would be useful for diagnosis of said disease." Thus, the recitations in the specification which indicate that the colon carcinoma associated antigens are not expressed in any other cancers are erroneous.

Other text erroneously indicates that the antigens have been found to be expressed *only* in colon, breast and ovarian cancer (see, e.g., column 3, lines 51-57), statements which are contradicted by Table 1 at column 23, which shows that mAb 31.1 bound to two out of three pancreatic cell lines tested, and Table 8 at column 28, which shows that mAb 31.1 bound to a stomach cancer cell sample.

Each of the erroneous statements regarding tumor specificity were made without deceptive intent. IBS believes that the defined antigens are not associated with all types of tumors, so that the statement "the antigens are tumor-specific, being present in the malignancies of colon, breast and ovarian cancer" (as found recited several times in the '657 patent specification, including at column 3 lines 33-35) remains true even if certain other types of cancer cells express the antigen. Similarly, the statement: "the immunogenicity in humans is specific, in that only colon, breast and ovarian cancer patients, but not patients with other forms of cancer, show evidence of specific in vivo or in vitro immunological reactivity to the antigens" (as found recited several times in the '657 patent specification, including at column 3 lines 39-43) was true at the time the specification was originally filed. However, data in the '657 patent

itself, and subsequent research, supports the conclusion that the antigen defined by at least monoclonal antibody 31.1 is not associated *only* with those cancers.

Further, it has been noted that claims 22, 23 and 47 contain an error, in that they relate to immunoassays for detecting the presence of colon carcinoma associated antigen in a sample. Both of these claims now recite steps for exposing the sample to antibody and then "detecting the binding of the antibody to the purified colon carcinoma associated protein antigen," which is an obvious error, since the antigen in the sample is not purified. This error in reciting "purified" was made without deceptive intent.

IBS is aware that during the prosecution of this reissue application, new deposits of true samples of the hybridomas PCA 31.1 and PCA 33.28, producing monoclonal antibodies 31.1 and 33.28, respectively, as referred to in the '657 patent, have been deposited with the ATCC under the terms of the Budapest Treaty, to correct the errors made in materials initially deposited with the ATCC.

IBS has reviewed and understands the amendments to the specification and claims of the '657 patent set forth in the RESPONSE submitted November 5, 2004 and the RESPONSE submitted herewith, which, among other things, (1) now recite the new ATCC accession numbers of the hybridoma cells deposited during the pendency of this reissue application; (2) focus the claims on monoclonal antibodies 31.1 and 33.28 and chimeric antibody Chi #1, antibodies that competitively inhibit the binding of these specific antibodies to their target antigens, and antibodies directed against the target antigens defined by these specific antibodies; (3) correct the erroneous statements relating to antigen specificity and purity of antigen in a sample; (4) correct various typographical errors; (5) refer to claimed antibodies that are not necessarily monoclonal antibodies as being "purified"; (6) specify that molecular weights were determined by gradient polyacrylamide gel electrophoresis; and (7) refer to purified antibody "raised against an immunopurified human colon carcinoma associated antigen".

Every error in the patent which is corrected in the present reissue application, and is not covered by a prior oath/declaration submitted in this application, arose without any deceptive intention.

VI. POWER OF ATTORNEY

IBS hereby appoints the following attorneys of the firm of Baker Botts L.L.P., having an address at 30 Rockefeller Plaza, New York, New York 10112 as their attorneys, with full power of substitution and revocation, to prosecute this reissue application and to transact all business in the Patent and Trademark Office connected therewith: Robert C. Sheinfeld, Reg. No. 31,300, Rochelle K. Seide, Reg. No. 32,300, Gary Butter, Reg. No., 33,841, and Lisa B. Kole, Reg. No. 35,225.

Please address all communications regarding this application to:

Lisa B. Kole, Esq.
Baker Botts L.L.P.
30 Rockefeller Plaza
New York, New York 10112

VII. DECLARATION

IBS hereby declares that all statements made herein of its own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of the Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

International Bio-Immune Systems, Inc.

By: Andrew C. Webb

Andrew C. Webb

Chief Operating Officer

Date: 4/25/07

ASSENT BY ASSIGNEE

International Bio-Immune Systems, Inc. the assignee of the entire right, title and interest in United States Patent No. 5,688,657, entitled "MONOCLONAL ANTIBODIES AGAINST CARCINOMA-ASSOCIATED ANTIGENS AND USES THEREFOR," pursuant to the assignment recorded in the records of the United States Patent Office at reel 6895, frame 803, hereby assents to the filing of the reissue application for said Patent No. 5,688,657 that is attached to this Declaration, and confirms reissue applicant's offer to surrender the original '657 patent as stated therein, and to the appointment of power of attorney as stated therein.

International Bio-Immune Systems, Inc.

By: Andrew C. Webb

Andrew C. Webb

Chief Operating Officer

Date: 4/25/07